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Personalized T-Cell Immunotherapy for Renal Cell Carcinoma

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Institution Receiving Award: FRED HUTCHINSON CANCER RESEARCH CENTER
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TECHNICAL ABSTRACT

Background: Renal cell carcinoma (RCC) is the most common and lethal primary kidney malignancy in adults, leading to ~14,400 deaths in the U.S. annually. Common risk factors for RCC include hypertension, obesity, diabetes, and smoking all of which are endemic to active duty military and Veteran populations. While early stage RCC is surgically curable, for the ~30% of patients who present with advanced/metastatic disease, current "targeted" clinical therapies are palliative with uniform development of treatment resistance and disease progression. However, it has long been recognized that clear cell RCC (ccRCC) is potentially susceptible to complete eradication by systemic immunotherapies (e.g., interleukin-2 and anti-PD1 antibodies) occasionally resulting in long-term remissions. The remarkable recent clinical success of engineered T cells expressing chimeric antigen receptors (CARs) to achieve complete remissions of refractory acute leukemias and lymphomas has also created intense interest to extend engineered T cells as a therapeutic modality to solid tumor targets. Therefore, a physiologically relevant and personalized in vitro testing platform to model T cell therapy is an urgent need for ccRCC. Results obtained from cell lines often do not translate clinically due to artifacts related to long-term culture in vitro. Animal models and tumor xenograft systems are laborious and expensive, and they do not incorporate important human-specific components such as endothelial or immune cells. The Initiating PI (Akilesh) has recently generated an in vitro "RCC-on-a-chip" in which primary tumor cells induce spontaneous angiogenic sprouting in blood vessels. In parallel, the Partnering PI (Tykodi) has developed reagents/tools for engineered T cell therapy for ccRCC.

Objective: We seek to combine our basic research expertise in microphysiological mimetics (Initiating PI Akilesh) with our clinical expertise in ccRCC immunobiology (Partnering PI Tykodi) to develop a first-of-kind, fully human, vascularized, RCC-on-a-chip T cell immunotherapy platform.

Aims: To study the immunophenotype of tumor-derived endothelial cells using the RCC-on-a-chip;

To develop RCC-on-a-chip as a platform for interrogating CD8+ T cell recognition of 3D ccRCC spheroids using characterized tumor and vascular endothelial cell lines;

To develop RCC-on-a-chip as a platform for analyzing fully autologous primary tumor, vascular endothelium, and CD8+ effector cell interactions in an in vitro 3D culture system.

Study Design: In Aim 1, we will generate and analyze single cell-level gene expression data from primary tumor-derived and control normal kidney microvascular endothelial cells from multiple patients to reveal the expression signatures that modulate T cell homing, adhesion, and activation. We will then introduce primary tumor-derived vascular endothelial cells into the ccRCC-on-a-chip to create a fully human, patient-specific platform. We will study the differences in barrier integrity, marker expression, and interactions of T cells with tumor-derived vs. normal microvascular endothelial cells using 3D confocal imaging. These studies will synergize with experiments in Aim 2 in which we will model antigen-specific T cell homing and killing of a model cell line in the ccRCC-on-a-chip. In initial experiments, we will omit the endothelial cell barrier and test numerous variables (e.g., flow rates, cell seeding densities and configurations, co-administration of checkpoint inhibitors, cytokines, or epigenetic modulators) to establish ideal conditions for tumor killing by primary T cells transduced with a tumor antigen-specific T cell receptor. We will then incorporate human umbilical vein endothelial cells to reconstitute the endothelial cell barrier and test antigen-dependent T cell migration and killing of tumor cells. Lastly, in Aim 3, we will translate our experience from the above studies to incorporate fully autologous patient-specific primary tumor cells, tumor-derived endothelial cells, and engineered tumor-reactive T cells into the RCC-on-a-chip. In all Aims, we will develop quantifiable outcome metrics for the chip platform to understand T cell migration and target cell-directed cytotoxicity.

Impact: Our proposal combines the basic research and clinical expertise of the PIs to establish a framework for studying ccRCC biology in a relevant in vitro biological system. We will develop an innovative tool, RCC-on-a-chip, to assess several key regulatory points that will impact delivery of effective T cell immunotherapy to patients with advanced ccRCC. These include engineering high numbers of tumor-reactive T cells by TCR gene transfer; T cell migration across tumor-associated endothelium; T cell chemotaxis toward tumor spheroids; and T cell cytotoxicity for ccRCC tumor cells in an antigen-restricted manner. Taken together, this system represents a compelling preclinical model for interrogating the therapeutic delivery of tumor antigen-specific T cells for advanced ccRCC and will provide a fertile medium to bidirectionally translate future clinical and experimental findings.

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